REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 14, 19 and 26-28 are pending in this application. Claims 14, 18-20 and 26 have been rejected. Claims 14 and 26 have been amended and new claims 27 and 28 has been added. Support for the amendment to claim 14 appears in original claim 26 and the specification at, *e.g.*, page 3, lines 12-16; page 13, lines 11-19; page 18, lines 14-15; and page 20, lines 19-21. Support for new claims 27 and 28 appears in as filed claim 14 and the specification at, *e.g.*, page 18, lines 27-29. Applicants have cancelled claims 18 and 20. No new matter is added.

OBJECTIONS

RestrictionRequirement/Species Election

Claim 14 has been amended to delete non-elected inventions (HSP 60/65 and B_2GP-1) as requested by the Examiner (*See*, Office Action at page 2). Applicants reserve the right to pursue the subject matter of these inventions in a later application.

Rejection under 35 U.S.C. §132

The Examiner has objected to the abstract filed April 23, 2002 under 35 U.S.C. §132 for introducing new matter into the disclosure (*See*, Office Action at pages 2-3). Applicants have amended the abstract to delete "the composition being formulated for inducing oral tolerance". Therefore, Applicants respectfully request that this objection be withdrawn.

REJECTIONS

Rejection under 35 U.S.C. §112, first paragraph

Written Description

Claims 14, 18-20 and 26 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner states there is no support in the specification as originally filed for the recitation of the phrase, "wherein said administration is in a sufficient amount to induce production of TGFβ, to suppress IFN-γ, and to suppress a type 1 T-cell cytokine pattern" in claim 14 (*See*, Office Action at pages 3-4). Claims 18 and 20 have been cancelled. The rejection is traversed to the extent it is applied to the pending claims 14, 19 and 26-28 as amended and added herein.

Applicants have amended claim 14 herein to recite "...wherein said administration is in a sufficient amount to induce production of IL-10 or TGFβ and to suppress IFN-γ..." The specification discloses that strong expression of IFN-γ is correlated with atherosclerotic lesions, and that the stimulation and production of IL-10 or TGFβ induces immune tolerance and can result in a reduced rate of atherosclerosis progression. (*See*, Specification at page 3, lines 10-14, and page 13, lines 16-19). Further, Applicants have disclosed methods for determining the levels of IFN-γ, IL-10 and TGFβ in subjects treated with the active components of the present invention. (*See*, Specification at page 18, lines 14-15 and page 20, lines 19-21). Therefore, Applicants submit that claim 14, as amended herein, is fully supported by the instant specification, as are new claims 27 and 28, which also recite the fully supported phrase. Withdrawal of the present rejection is respectfully requested.

Enablement

Claims 14, 18-20 and 26 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner states that the "specification does not disclose how to use the claimed method in vivo in humans to treat or prevent disease" (*See*, Office Action at pages 4-6). Claims 18 and 20 have been cancelled. The rejection is traversed to the extent that it is applied to the pending claims 14, 19 and 26-28 as amended and added herein.

The Examiner has the burden to establish a reasonable basis to question the enablement for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); M.P.E.P § 2164.04. Under 35 U.S.C. § 112, first paragraph, lack of enablement is found only if one reasonably skilled in the art could not make or use the invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *See United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Even if the experimentation required is complex, it is not necessarily undue if artisans skilled in the relevant art typically engage in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm. 1983).

The Examiner has not met this burden, in fact, the Examiner has not produced any evidence at all. The Examiner has asserted that the as-filed specification lacks working examples under one factor of the *Wands* test. The Examiner stated that although the specification provides an example of a mouse model demonstrating that the oral tolerance-inducing composition of the present invention would be effective, other mouse research has shown that although oral tolerance has been shown to be effective in treating multiple sclerosis and rheumatoid arthritis, these diseases were not successfully treated in humans using oral tolerance. Applicants submit that the LDL-receptor (LDLR) deficient mouse is the most art-recognized model of the biochemical and morphological effects of atherosclerosis. As such, Applicants have provided several working examples, and demonstrated successful prevention or treatment of atherosclerosis by administration of an immunological oral tolerance-inducing composition of the present invention. (*See*, 37 C.F.R. §1.132 Declaration of Dror Harats and corresponding Appendix 1 ("Harats Declaration"); and Specification at, *e.g.*, page 15, lines 20-29; and page 18, line 18 to page 19, line 31).

Enablement is determined by reference to the state of the art at the time of the patent application, rather than at some later time. *Wright*, 999 F.2d at 1562. The use of animal models (i.e. murine models) to evalulate the effects of pharmacologic agents on atherosclerosis was well recognized in the art when the instant application was filed. (*See* Bocan, 1998. Animal models of atherosclerosis and interpretation of drug intervention studies. Curr. Pharm. Des. 4(1):37-52). Specifically, the LDLR deficient mouse was recognized in the art as a preferred model of atherosclerosis at the time of the instant application. (*See* Ishibashi et al., 1993.

Hypercholesterolemia in low density lipoprotein receptor knockout mice and its reversal by adenovirus-mediated gene delivery. J Clin Invest. 92:883–893; Lichtman *et al.*, 1999. Hyperlipidemia and atherosclerotic lesion development in LDL receptor-deficient mice fed defined semipurified diets with and without cholate. Arterioscler. Thromb. Vasc. Biol. 19(8):1938-44; Maron, R. *et al.*, 2000. Mucosal administration of HSP 65 decreases atherosclerosis and inflammation in the aortic arch of LDL receptor deficient mice. FASEB J. 14:A1199-(Abstr.)). Moreover, mice having targeted inactivation of the apolipoprotein E (ApoE) gene and of the LDLR gene, under appropriate conditions, develop complex atherosclerotic lesions and provide practical atherosclerotic mouse models and are the most utilized model to study lipids and atherosclerosis (*See*, Harats Declaration, paragraphs 11 and 12).

Applicants also traverse the Examiner's contention relating to another factor of the *Wands* test. The Examiner has asserted that the specification does not disclose the doses to be used to induce the functional parameters recited in pending claim 14 (*See*, Office action, page 6). Applicants note that the specification provides a range of concentrations of the immunological oral tolerance-inducing composition that induce production of IL-10 or TGF-β and suppress IFN-γ (*See, e.g.*, page 18, lines 27-29; page 19, lines 18-19). Moreover, studies using the teachings of the instant specification have shown that oral administration of OxLDL or an oxidized derivative of OxLDL to mice induce an anti-inflammatory response and showed suppression of IFN-γ (*See*, Harats Declaration, paragraphs 13 and 14, and Appendix 1, Fig. 1-4). Therefore, Applicants assert that one of ordinary skill in the art, using the teachings of the instant invention, would be able to determine the corresponding doses useful in other species, including humans, without undue experimentation. The specification need not disclose what is well known in the art. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 U.S.P.Q. (BNA) 81, 94 (Fed. Cir. 1986).

For the above-stated reasons, Applicants submit that pending claims 14, 19 and 26-28 meet the enablement requirement of 35 U.S.C. §112, first paragraph, and request this rejection be withdrawn.

Rejection under 35 U.S.C. §102(b)

Claims 14, 18 and 20 are rejected under 35 U.S.C. §102(d) as anticipated by U.S. Patent No. 4,874,795 to Yesair ("Yesair"). Claims 18 and 20 have been cancelled. The rejection is traversed to the extent that it is applied to the amended claim 14 and new claims 27-28.

The Examiner states that Yesair teaches a composition for oral administration containing lysophosphatidyl choline (LPC), which the Examiner states is a modified low density lipoprotein (LDL) and also a derivative of OxLDL (*See*, Office Action at pages 6-7). Applicants have amended claim 14 to delete the phrases "modified low density lipoprotein" and "functional derivatives thereof." As such, amended claim 14 requires that the active components are OxLDL or malondialdehyde LDL (MDA-LDL). Yesair neither teaches nor suggests the use of OxLDL or MDA-LDL. Therefore, Applicants submit that Yesair does not anticipate claim 14, as amended herein.

Applicants submit that Yesair does not anticipate new claims 27 and 28. New claim 27 recites in part, "...consisting of modified low density lipoprotein..." Yesair only teaches the use of LPC, a modified low density lipoprotein as asserted by the Examiner, in the presence of other lipids, such as a non-esterified fatty acid (*See*, Yesair, col. 14). Yesair does not teach or suggest the use of LPC, or any other modified LDL, without the presence of other lipids. Therefore, Applicants submit that Yesair does not anticipate new claim 27.

New claim 28 requires that the active components are selected from the group consisting of "...human modified low density lipoprotein and human oxidized low density lipoprotein..." As discussed *supra*, Yesair does not teach or suggest the use of any oxidized LDL, much less human oxidized LDL. Further, Yesair neither teaches nor suggests the use of human modified LDL as Yesair only teaches LPC derived from soy lecithin (*See*, Yesair, the paragraph bridging columns 8 and 9). Therefore, Applicants submit that Yesair does not anticipate new claim 28.

Furthermore, studies have shown that esteric as well as etheric phospholipids, i.e. LPC (also referred to as Lysolectitin), as described by Yesair, are ineffective in reducing atherogenesis in mice when compared to OxLDL or and oxidized derivative of OxLDL (*See*, Harats Declaration, paragraphs 8 and 9, and Appendix 1, Fig. 1). Therefore, Applicants submit that Yesair teaches away from the present invention.

Applicants submit that claim 14, as amended herein, and claims 27 and 28, as added herein, are not anticipated by Yesair and respectfully request withdrawal of the present rejection.

CONCLUSION

On the basis of the foregoing amendment and remark, Applicants respectfully submit that the pending claims are in condition for allowance. Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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